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Catalytic asymmetric alkylation of ketones using organometallic reagents

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The catalytic asymmetric synthesis of tertiary alcohols by the addition of organometallic reagents to ketones is of central importance in organic chemistry. The resulting quaternary stereocentres are difficult to prepare selectively by other means despite their widespread occurrence in natural products and pharmaceuticals. Over the past few years, several seminal reports on the formation of chiral tertiary alcohols with excellent selectivities have appeared in the literature. This review records the major strategies and current status of the catalytic enantioselective synthesis of chiral tertiary alcohols using alkylation/arylation reactions with highly reactive organometallic reagents derived from Zn, Al, Mg and Li.

Introduction

Chiral enantiopure alcohols represent a key class of organic molecules due to their widespread occurrence in natural products, pharmaceuticals and their application as chiral building blocks in synthetic chemistry (Fig. 1a) [1–3]. Different strategies for the preparation of single enantiomers of chiral secondary alcohols comprise kinetic resolution, enantioselective desymmetrization, and asymmetric hydrogenation (both with enzymes and transition-metal catalysts). Recently, also the catalytic enantioselective conjugate addition of water has been reported [4–6]. Generating chiral tertiary alcohols is however particularly challenging [7]. Asymmetric hydrogenation is obviously not applicable for

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the formation of tertiary alcohols and the resolution of racemic tertiary alcohols with lipases or esterases is mostly not efficient. Therefore, methods for the synthesis of chiral tertiary alcohols rely mainly on the construction of carbon–carbon bonds [8–10].

The catalytic asymmetric addition of organometallic reagents to aldehydes and in particular to ketones is one of the most straightforward methods for carbon–carbon bond formation (Fig. 1b) [11,12]. Over the years, the catalytic asymmetric addition of organometallic reagents to aromatic aldehydes affording secondary alcohols has been well developed [13]. Catalytic asymmetric addition of organometallic reagents to ketones is considerably more challenging. The difficulties are associated with a significantly diminished reactivity of ketones compared to aldehydes, and a decreased enantiodiscrimination due to the smaller steric and electronic differences between the two substituents on the carbonyl group.

Discussion

To overcome the lower reactivity of ketones, the use of highly reactive organometallic compounds such as Grignard and organolithium reagents has been explored [11–15]. However, these reactive organometallics are intrinsically nucleophilic and can add to carbonyl compounds without the aid of a catalyst, resulting in a racemic background reaction. In addition, these reagents are strong bases as well and give rise to the formation of side products due to enolisation.

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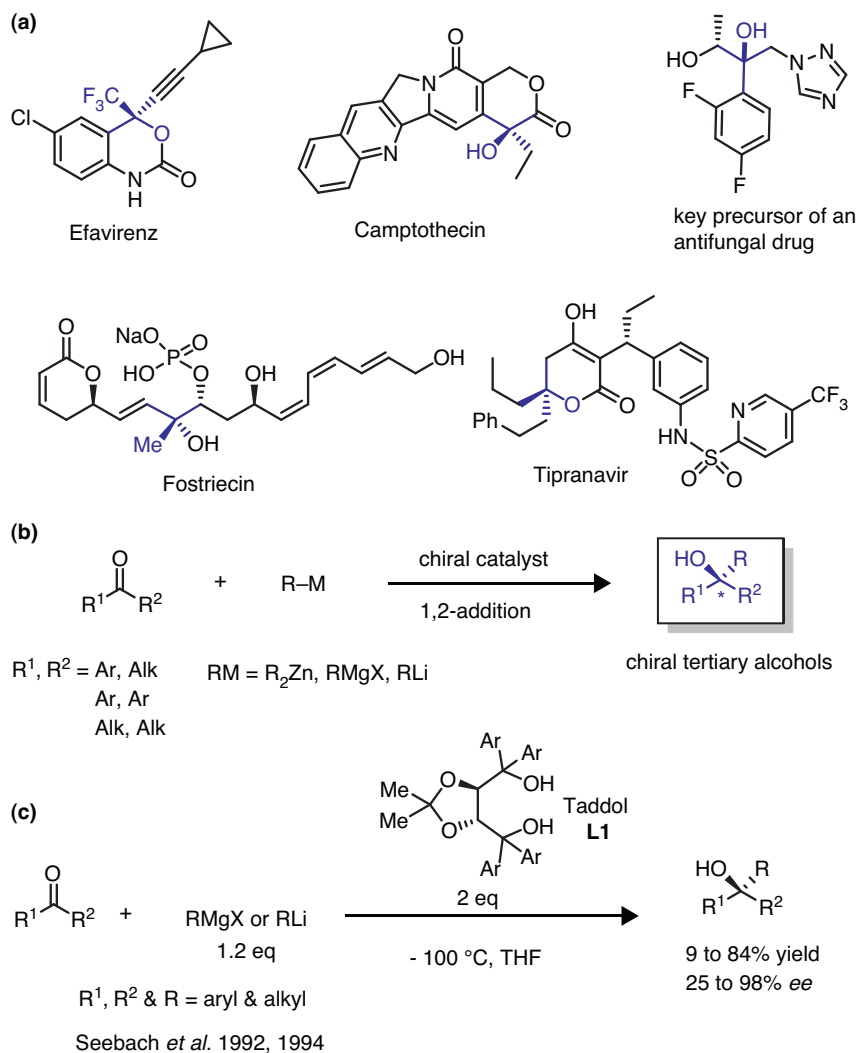


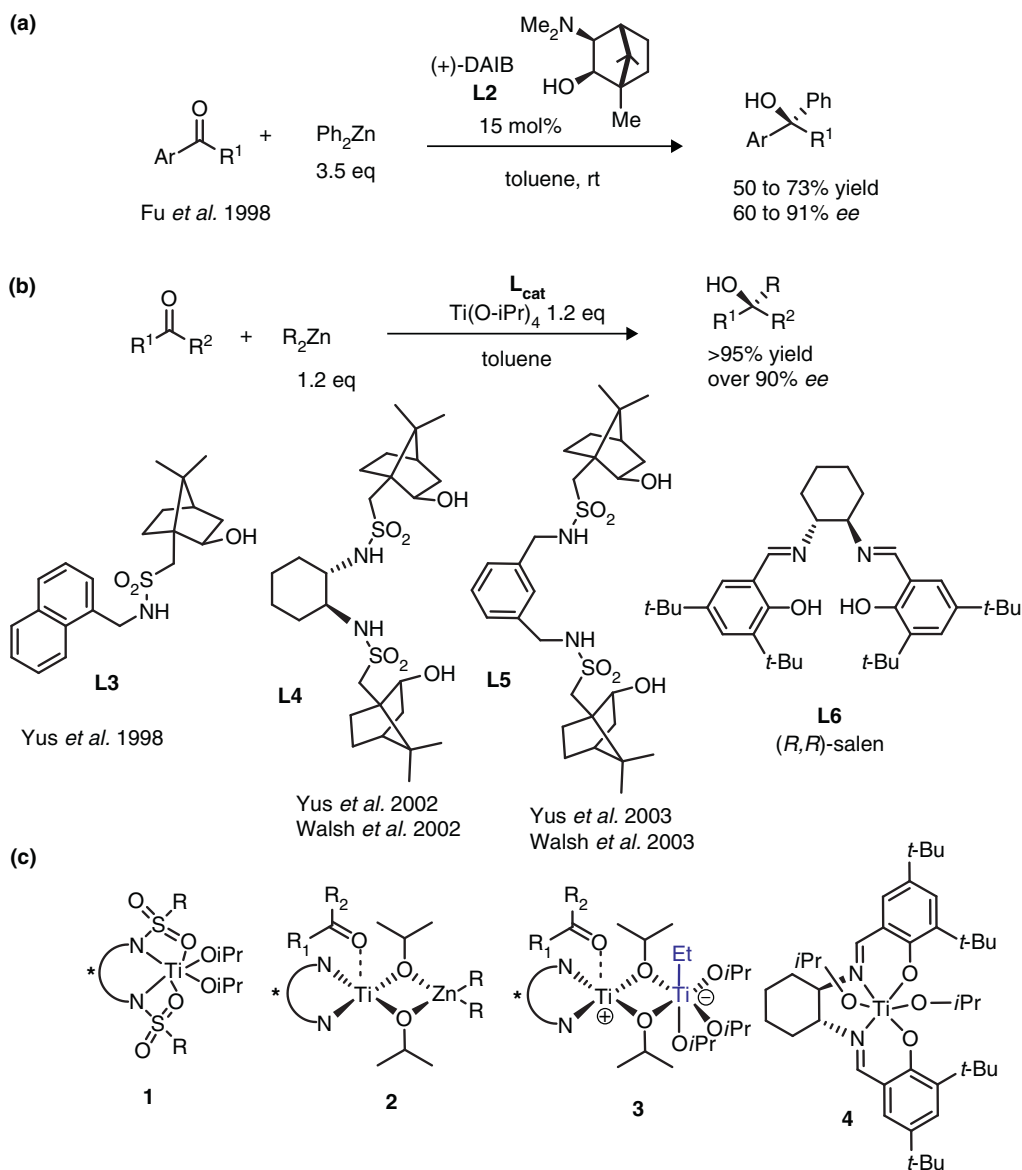
Figure 1. (a) Pharmaceutically active molecules bearing chiral tertiary alcohol moiety. (b) Asymmetric addition of an organometallic to an achiral ketone. (c) Asymmetric addition of Grignard and organolithium reagents to ketones.

For alkyl Grignard and lithium compounds containing β -hydrogens, also reduction of the carbonyl group is a serious complication. Therefore, the enantioselective addition of these reagents to both ketones and aldehydes required, until recently, at least one equivalent of a chiral ligand (Fig. 1c) [16]. A variety of organotitanium reagents, prepared *in situ* by transmetalation of $\text{ClTi}(\text{O-}i\text{Pr})_3$ using Grignard and organolithium reagents, have been used successfully as well, after the strict removal of magnesium and lithium salts [17,18]. However, the development of a catalytic reaction has been hampered by the high reactivity of these organometallic reagents.

An important alternative to reduce the amount of chiral ligand is the use of, much less reactive, organozinc reagents [19]. To add to ketones, organozinc reagents require Lewis acid activation of the carbonyl group, chiral Lewis base activation of the organozinc reagent, or a combination of

both strategies. In 1998, Dosa and Fu reported the first example of a catalytic asymmetric addition of diphenylzinc to ketones, catalyzed by 3-exo-(dimethylamino)isoborneol (DAIB, **L2**, Fig. 2a) [20–22]. Shortly thereafter, Yus and co-workers reported the first catalytic asymmetric addition of dialkylzinc reagents catalyzed by hydroxycamphorsulfonamide ligand **L3** (Fig. 2b) in the presence of titanium tetraisopropoxide [23].

In 2002, Walsh' group and Yus' group independently reported trans-1,2-bis(hydroxycamphorsulfonamido) cyclohexane **L4** as an excellent promoter for the enantioselective addition of dialkylzinc reagents to ketones in the presence of titanium tetraisopropoxide (Fig. 2b) [24,25]. In addition, diarylzinc reagents as well as α,β -unsaturated ketones were successfully employed using this ligand. These results inspired the design of improved ligand **L5** (Fig. 2b) for the asymmetric 1,2-addition of dialkylzinc reagents to ketones



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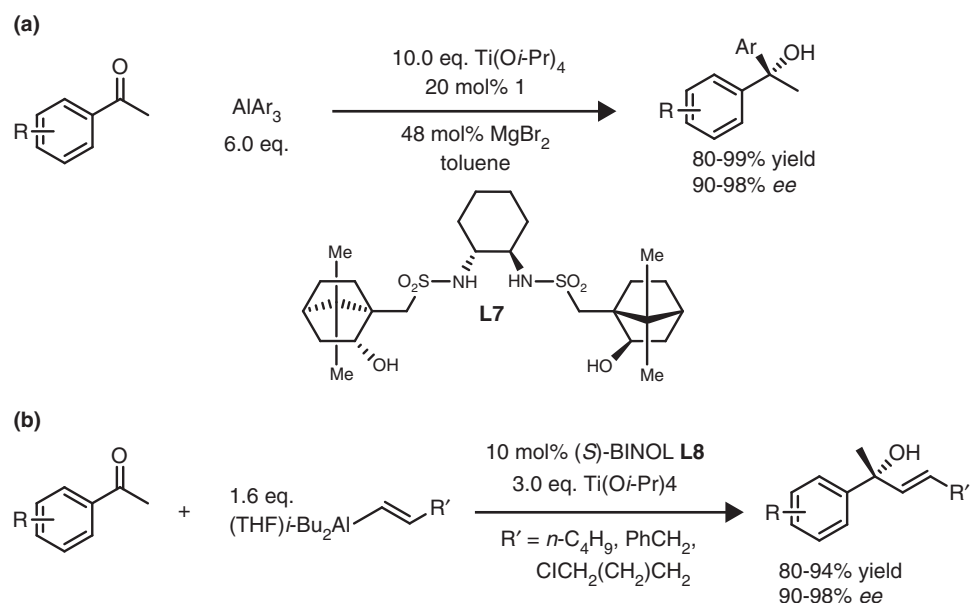
Figure 2. (a) Catalytic asymmetric diphenylzinc addition to ketones. (b) Diethylzinc additions to ketones in the presence of $\text{Ti}(\text{O}i\text{Pr})_4$. (c) Proposed key active species involved in the reaction of diethylzinc additions to ketones.

[26,27]. The catalytically active species for dialkylzinc addition reactions using sulfonamide ligands has been postulated to be a dinuclear titanium complex or in some cases a titanium–zinc complex in which one titanium atom bears the chiral ligand and the ketone and the other titanium atom (or zinc atom) the alkyl moiety. The two metal centres are connected by two isopropoxy bridges (Fig. 2c).

A common feature of these reactions is the necessity to employ equimolar amounts or an excess of titanium tetraisopropoxide to achieve good selectivities. It is believed that addition of organozinc reagents to non-reactive ketones proceeds via *in situ* formation of alkyltitanium species which are in principle less reactive than Grignard reagents however

superior to dialkylzinc reagents (Fig. 2c). This hypothesis is supported by a recent report from Li *et al.* on the direct addition of alkyltitanium reagents to aldehydes catalyzed by a chiral titanium catalyst derived from H8-BINOL [28]. In one case it was possible to carry out the reaction using 60 mol% of titanium tetraisopropoxide [29]. In another case it was reported that $\text{Ti}(\text{O}i\text{Pr})_4$ -free 1,2-addition to aromatic ketones is possible when a 3-fold excess of organozinc reagent is used [30].

In the case of ketoesters, which are more reactive than normal ketones, catalytic amounts of titanium tetraisopropoxide are sufficient. Kozłowski and co-workers designed a chiral salen **L6** (Fig. 2b) ligand capable of catalyzing the



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Figure 3. Asymmetric Ti(IV)-catalyzed addition on aryl methyl ketones using (a) aryl aluminum reagents and (b) alkenyl aluminum reagents.

addition of organozinc reagents to ketoesters in the presence of 10 mol% of titanium tetraisopropoxide [31]. It was proposed that this chiral salen ligand is able to chelate at the same time one titanium atom, following alkoxy interchange on titanium tetraisopropoxide, and one zinc atom, through coordination of the nitrogen atom by diethylzinc thus providing bifunctional alkylation.

These discoveries have permitted the development of an array of methods for the addition of organozinc reagents to aromatic ketones, enones and ketoesters [12,13,32]. Nevertheless, diorganozinc reagents have an inherent drawback crucial to practical applications [33,34]. In their standard method of preparation, zinc oxidatively adds to alkyl iodides leading to alkylzinc iodides, which after distillation or sublimation, provide dialkylzinc reagents. Due to the thermal instability of their higher homologs, this method is applicable only to diorganozinc reagents with small alkyl groups. Therefore, only few organozinc reagents are commercially available. To circumvent this intrinsic problem, several methods for preparing diorganozinc reagents, including functionalized analogues, have been developed by the groups of Knochel [33] and Charett [34].

The successful 1,2-addition of organozinc reagents to ketones contrasted strongly with the few examples of the addition of organoaluminum reagents to ketones. These examples are limited mostly to arylation reactions (Fig. 3a) [35–37]. In 2007 Gao and coworkers reported the first example of the asymmetric addition of arylaluminum reagents to ketones catalyzed by a titanium catalyst of (S)-BINOL **L8** (Fig. 3b). Good yields and enantioselectivities up to 97% were

achieved for a variety of alkyl aryl ketones. Also in this case, an excess of organoaluminum reagent as well as a super-stoichiometric use of titanium tetraisopropoxide is required.

Readily available Grignard reagents have only been used in combination with stoichiometric amounts of a chiral ligand (Fig. 1c). This is not surprising, as the uncatalyzed addition of the Grignard reagent is a formidable competitor. Indeed, catalytic non-asymmetric addition of Grignard reagents to ketones has become possible only recently using Zn(II) salts as catalyst [38]. In 2008 Harada *et al.* reported that highly enantioselective catalytic addition of Grignard reagents to aldehydes is possible, albeit requiring the use of excess titanium tetraisopropoxide, most probably via formation of organotitanium reagents as nucleophiles [39,40].

This was the status in 2011 when we reported the first enantioselective catalytic addition of Grignard reagents to ketones (Fig. 4a, b). Initial results in the addition of Grignard reagents to enones were obtained employing a catalytic system very unusual for this class of reactions. Copper bromide in combination with chiral Josiphos-type diphosphine ligand **L9** was found to be an excellent catalyst providing chiral tertiary allylic alcohols in relatively short reaction times, with high yields and ee's, and without additional Lewis acid activation (Fig. 4a) [41]. The results demonstrated that the longstanding paradigm of Cu(I) based catalysts favoring 1,4-selectivity over 1,2-selectivity in the addition of organometallic reagents, known since 1941, is not fully justified [3,42–44]. It was shown that the α -substituent and the presence of a double bond in the substrate play a crucial role in obtaining high regio- and enantioselectivity and that highest

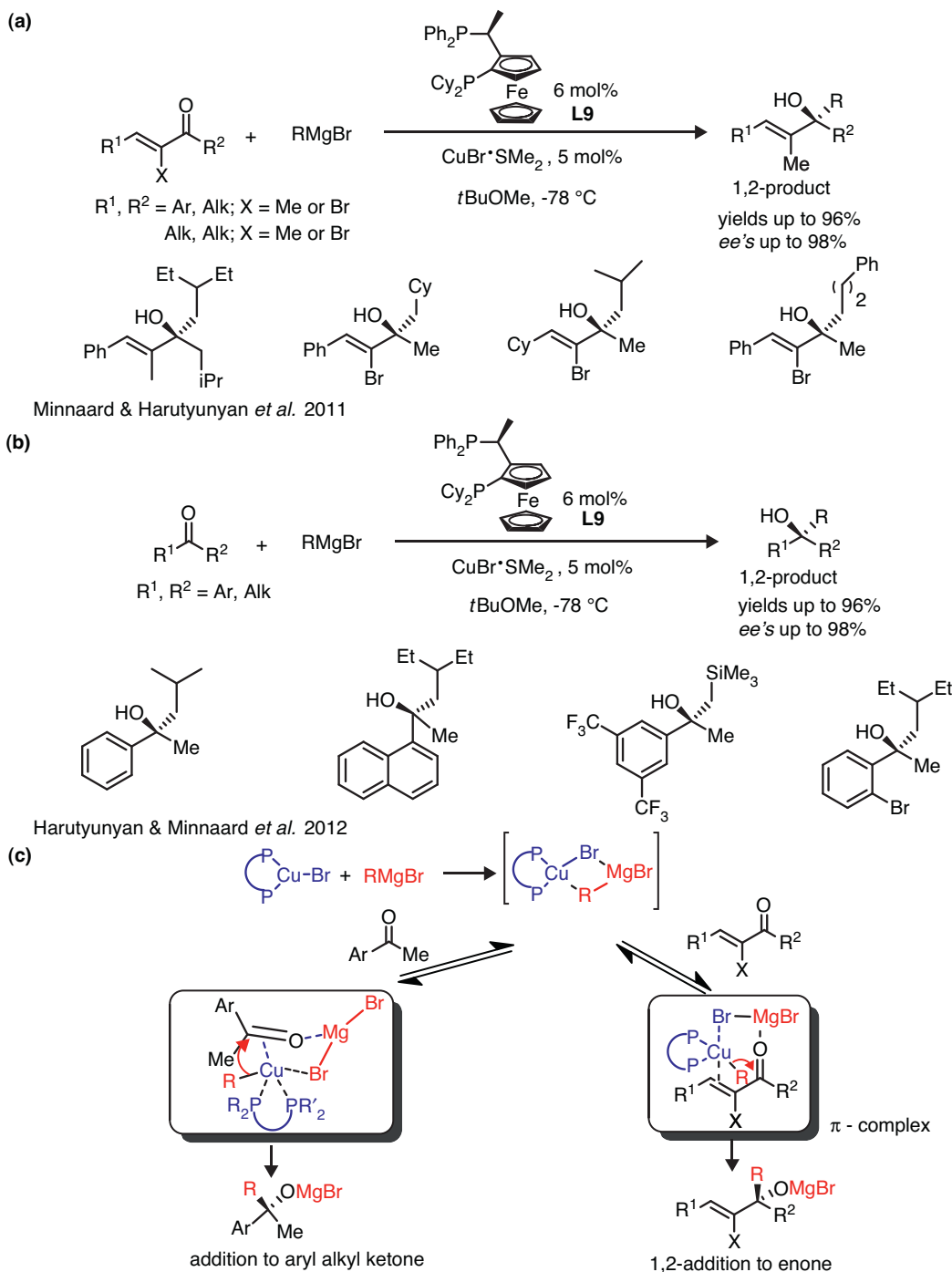


Figure 4. (a) Copper(I) catalyzed asymmetric addition of Grignard reagents to α,β -unsaturated α -substituted ketones. (b) Copper(I) catalyzed asymmetric addition of Grignard reagents to aromatic ketones. (c) Proposed catalytically active species involved in copper(I) catalyzed asymmetric addition of Grignard reagents to α,β -unsaturated and aryl alkyl ketones.

enantioselectivities are obtained with branched, so bulky, Grignard reagents. To access also tertiary alcohols *without* a substituent at the α -position, the addition to α -brominated enones was developed [45]. After 1,2-addition, the products are readily debrominated, thereby providing a formal 1,2-addition to α -H substituted enones in excellent selectivities.

In a subsequent report, it has been shown that this Cu(I)-based catalytic system can also be successfully applied in the addition of Grignard reagents to aryl alkyl ketones (Fig. 4b) [46]. To explain the reactivity of Cu(I) based catalysts in the addition of Grignard reagents to enones and aryl alkyl ketones, different activation modes can be considered

(Fig. 4c). The first step in both cases is the transmetalation of Cu(I)-complex by the Grignard reagent. In the case of enones, the alkyl-Cu(I)-complex is capable to activate the ketone through π -complexation with the conjugated double bond, whereas Mg^{2+} acts as a Lewis acid and activates directly the carbonyl moiety [46]. In the case of aryl alkyl ketones, this double activation occurs via a π -complex between the double bond of a carbonyl moiety and Lewis acid activation of that carbonyl moiety via the Mg^{2+} ion.

Conclusions

Over the years, the catalytic asymmetric addition of organometallic reagents to ketones has become a reliable method for the synthesis of chiral tertiary alcohols with high enantioselectivity.

An important challenge in asymmetric catalysis. From the available pool of organolithium, organomagnesium, organoaluminum and organozinc reagents, significant progress in asymmetric 1,2-addition reactions has been made mainly with latter ones. Recent advancements, however, allow to open a new page in this research by using readily available Grignard reagents in the catalytic asymmetric addition to ketones. The three strategies based on organozinc, organoaluminum and organomagnesium should be viewed as being complementary.

High enantioselectivities can be obtained with both diaryl- and dialkylzinc reagents using readily available chiral ligands. Importantly, functionalized organozinc reagents also can be used. However, dialkylzinc reagents are less accessible compared to Grignard reagents, the reactions commonly take long time to complete and are restricted to linear alkyl chains. Furthermore, an equimolar amount of titanium tetraisopropoxide is required in most of the reactions using organozinc and organoaluminum reagents. The more accessible and inexpensive Grignard reagents are also capable of providing high levels of enantioselectivity and high yields; the reactions are normally completed within a few hours and additives are not required. The highest enantioselectivities are obtained with branched alkyl chains, both in substrate and Grignard reagent, which complements the organozinc and organoaluminum reagents. Considering scale up, an advantage of Grignard reagents over organozinc and organoaluminum reagents is the transfer efficiency of the alkyl group. In the case of Grignard reagents, there is 100% transfer of the alkyl group to the ketone while using organozinc and organoaluminum reagents, 50% and 66% are wasted, respectively. Despite this recent progress in the addition of Grignard reagents still considerable research is needed to increase the enantioselectivities with Grignard reagents bearing aryl or linear alkyl chains, which currently are moderate or even absent.

Major challenges still remain in the substrate scope as well, such as achieving high enantioselectivity with alkyl alkyl

ketones and aryl aryl ketones. Furthermore, the catalytic enantioselective addition to ketones or aldehydes using readily available organolithium reagents still has to be developed. Nevertheless, continued exploratory research can address these challenges and provide more practical methods for carrying out catalytic asymmetric reactions using various organometallic reagents and both activated and non-activated ketones.

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